TABLE

SERUM PENICILLIN LEVELS AFTER INTRAMUSCULAR

Author and Date	Preparation Dose	Serum Penicillin Levels											
		1 hr			2–3 hrs			3 hrs			4 hrs		
		No. of Patients	Average	Range	No. of Patients	Average	Range	No. of Patients	Average	Range	No. of Patients	Average	Range
Tommila and Savolainen (1955)	Aqueous Procaine Penicillin (600,000 units)	—	—	—	47	0·56	0·14 to 1·64	—	—	—	—	—	—
Rein, Buckwalter, Mann, Landy, and Flax (1953) Total Patients 50	"Panbiotic"† (1,200,000 units)	25	3·185	0·5 to 4·6	—	—	—	13	1·5	0·2 to 2·9	31	0·94	0·25 to 2·05
	P.A.M.* (1,200,000 units)	—	0·46	—	—	—	—	—	—	—	—	—	—
	"Panbiotic"*† (1,200,000 units)	—	3·18	—	—	—	—	—	—	—	—	—	—
	Benzathine Penicillin* (600,000 units)	—	0·17	—	—	—	—	—	—	—	—	—	—

* Figures shown were read from graph.

(2) These strains show 19·5 per cent. of gonococci with sensitivities between 0·125 and 0·5 units of penicillin per ml.

(3) Post-treatment gonorrhoea in the first week after 300,000 units of aqueous procaine penicillin or P.A.M. had been given occurred mainly at these sensitivity levels and in no proven case below 0·03 units/ml.

(4) It is suggested that 600,000 to 1,200,000 units aqueous procaine penicillin injected intramuscularly should be the routine dose for acute gonorrhoea, but that efforts should be made to devise a preparation of penicillin which would give a blood level of not less than 1 unit/ml. for not less than 24 hrs, and, preferably, for not much longer, owing to the risk that long-lasting low levels of penicillin may produce more resistant strains of gonococci or asymptomatic carriers.

Penidural A.P. and L.A. are names used by John Wyeth and Brother, Ltd., to whom one of us (F.R.C.) is greatly indebted for supplies of both preparations. Our thanks are due also to Dr. G. R. Fryers, Medical Adviser to that Company.

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DISCUSSION

The President, DR. S. M. LAIRD (*Manchester*), congratulated both openers on their papers and said that, from the point of view of epidemiology and treatment policy, these two papers were perhaps the most important that the Society had listened to for some considerable time. It was often difficult to decide whether the persistence of urethritis and gonococci represented treatment failure or re-infection, and the position with regard to gonorrhoea was becoming reminiscent of the early days of the penicillin treatment of early syphilis when relapse versus re-infection was hotly debated. It was clear that *quantitative* sensitivity tests as developed and described by Dr. Wilkinson were essential in these cases in the same way as quantitative serological tests were important in the management of early syphilis. Dr. Curtis was most

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INJECTION OF LONG-ACTING PENICILLIN PREPARATIONS

(units/ml.) after so many Hours

6 hrs			9 hrs			10 hrs	12 hrs			20 hrs	24 hrs		
No. of Patients	Average	Range	No. of Patients	Average	Range	Average	No. of Patients	Average	Range	Average	No. of Patients	Average	Range
47	0·34	0·07 to 0·8	—	—	—	—	47	0·2	0·07 to 0·3	—	47	0·15	0·07 to 0·25
13	0·61	0·1 to 1·7	13	0·36	0·07 to 1·05	—	49	0·28	0·05 to 0·67	—	37	0·19	0·04 to 0·41
—	—	—	—	—	—	0·4	—	—	—	0·35	—	—	—
—	—	—	—	—	—	0·5	—	—	—	0·22	—	—	—
—	—	—	—	—	—	0·16	—	—	—	0·15	—	—	—

† "Panbiotic" = Penidural A.P. (See footnote page 78)

fortunate in having these special facilities available. The President had met his first case of resistant gonorrhoea early in 1944 before he himself had had the opportunity of using penicillin; a maritime anti-aircraft gunner infected in England before sailing in convoy had been given penicillin on arrival in the U.S.A. and again aboard the ship which brought him back to England. Neither course of penicillin proved effective and, on admission to the Military Hospital, Preston, the patient still had acute gonorrhoea which responded rapidly to sulphonamides. Although cultures were not done and at that time some batches of penicillin were of poor quality, it seems likely that this was an isolated example of penicillin-resistant gonorrhoea. Such isolated cases did not cause concern and had been noted from the outset of suphonamide treatment. However, when one case in every five showed increased resistance to penicillin, the situation was disturbing.

DR. J. E. CRADDOCK-WATSON (*St. Bartholomew's Hospital, London*) reported his findings during the past 6 months. The sensitivity of strains of gonococci from 200 patients had been tested to penicillin, streptomycin, and sulphathiazole. 158 of the strains were inhibited by 4 μg. streptomycin per ml. and all by 16 μg./ml. Only one strain needed more than 8 mg. sulphathiazole per 100 ml. for inhibition. 38 strains needed 0·128 unit or more of penicillin per ml. for inhibition, and patients infected with these strains relapsed after treatment more often than those infected with more sensitive strains (34 to 7 per cent.). (Craddock-Watson, Shooter, and Nicol, 1958).

DR. G. L. M. MCELLIGOTT (*London*) thanked the speakers for their most interesting papers. The situation at St. Mary's Hospital was much the same as at The London Hospital. During the period 1950–54, all cases of gonorrhoea in men had been treated with 125,000 units P.A.M. by intramuscular injections with excellent results, on the assumption that this dose would give levels in the serum of 0·03 unit per ml. for from 12 to 24 hrs, and would not mask incubating syphilis.

In 1954 the results became less satisfactory; this coincided with the arrival of large numbers of immigrants. The dosage had then been raised to 300,000 units P.A.M. for men as well as for women.

During 1955, the results, particularly in men, gradually worsened, and by that date promiscuous immigrants predominated amongst the male patients.

In 1956, following results announced at a Symposium in the United States of America, 600,000 units benzathine penicillin was used in the treatment of all female patients, in the hope that this might both cure the gonorrhoea and protect against re-infection. Study showed, however, that, of 100 cases treated in this way, no less than forty need re-treatment. Since then the male cases had been treated with 600,000 units aqueous procaine penicillin and the females with two injections of 600,000 units, given on successive days. At this point Dr. Marston had begun to carry out sensitivity tests and, on comparatively small numbers, her results were very much the same as those announced.

What had been heard that evening was important, because the number of new cases of gonorrhoea in both men and women was rising each quarter. He had been interested to hear from Dr. Craddock-Watson that sulphathiazole was getting back to its old form. It should be remembered, however, that 15 per cent. of cases had been resistant to sulphonamide therapy *ab initio*, and that universal sulphonamide treatment would again result in the spread of resistant strains.

DR. N. A. MARSTON (*St. Mary's Hospital, London*) said that she had started testing for penicillin resistance of the gonococcus at St. Mary's Hospital in the early part of 1957. The method first used consisted in filling cups with penicillin solutions of varying concentrations and finding whether the gonococcus was inhibited in its growth around those cups. It had since been seen that this method was very

inaccurate, as the actual concentration of penicillin to which the gonococcus was resistant was very much less than the concentration of penicillin which allowed growth of the organism up to the cup margins. 22 cases tested by this method were found to be resistant to as much as 5 or 3 units/ml. penicillin; by comparing this method with the more accurate tube technique it was thought that these high levels actually represented a resistance of the gonococcus to approximately 0·1 unit/ml. penicillin.

After the inaccuracy of the cup technique was appreciated a further eleven cases which had failed to respond clinically to penicillin were tested by the tube technique. Nine of these cases showed resistance to a level of 0·1 units/ml. penicillin and two to 0·25 units/ml. penicillin.

DR. E. E. PREBBLE (*Liverpool*) said he had listened to the papers with considerable interest and added his congratulations. So far as Liverpool was concerned, he could not give figures which would be of any help since in the main clinics the routine treatment for males consisted of streptomycin only and that for females consisted of penicillin with the addition of Sulphathiazole A definite resistance to streptomycin was taking place and the figures had risen in 3 years from 2·3 to about 7 per cent. One case of true resistance to penicillin even in large doses had occurred at one of the outlying centres but this was the only case known on Merseyside.

DR. W. V. MACFARLANE (*Newcastle-upon-Tyne*) remarked on the relatively infrequent occurrence of penicillin resistant gonorrhoea in the Newcastle clinic. He recalled only three patients and one was of particular interest. Acquiring an extra-marital infection, she infected her husband and when examined at the initial visit presented no gonococcal complications. An injection of 0·6 mega units "Benapen" failed to cure the gonococcal infection and two more similar injections daily likewise met with no success. With a view to excluding the possibility of re-infection, she was admitted to the ward where she received 1 mega unit penicillin without success. The subsequent administration of Terramycin 250 mg. orally 6-hrly cleared the condition in less than 24 hours.

Further interesting points emerging from this case record were:

(*a*) The initial dosage resulting in failure in the case of the wife produced cure in the husband, as it did in her consort;

(*b*) The laboratory reported that the gonococcus appeared to show no evidence of penicillin resistance.

DR. R. R. WILLCOX (*London*) confirmed what Dr. McElligott had said. In spite of increasing doses of repository penicillin given through the years, the failure rates at St. Mary's, Paddington, had risen steadily, until with doses as high as 1·2 mega units failure rates of 17·9 per cent. had been experienced in a sample series treated with P.A.M., and as high as 30·3 per cent. in cases treated with benzathine penicillin. The interesting fact was that the failure rates experienced in Negroes were double those seen in white patients. This did not apply only to penicillin given by injection but also to streptomycin and penicillin given by mouth. In a series of 85 cases of phenoxymethyl penicillin given orally, there had been no failures in white persons but no less than 28·6 per cent. of failures in Negroes. It was possible, therefore, that lessened sensitivity to penicillin was being fostered by more rapid passage and by repeated exposure of the gonococcus to penicillin in this ethnic minority. The ideal curve of penicillinaemia, suggested by Dr. Curtis for the treatment of gonorrhoea, could theoretically be achieved by repeated injections of shorter-acting penicillins and by cutting it off with penicillinase. These problems had recently been discussed at the World Health Organization V.D. Seminar in Tokyo which Dr. Willcox had been fortunate to attend. It was evident there that the experience of higher failure rates to increasing doses of penicillin was widespread throughout the Far East. Indeed, he had visited a so-called Sex Store in Yokohama where, on learning that the tetracycline antibiotics were being prescribed for gonorrhoea and enquiring the reason for this, he had been told that penicillin was no longer effective! It was agreed at the W.H.O. Conference that a higher penicillin serum level was required to provide a greater "hurdle" against the development of further resistance and that for this quicker-acting preparations were necessary. The use of quicker-acting preparations, however, would mean a greater likelihood of serious penicillin sensitization reactions and the sacrifice of the penicillin "tail" obtained with repository penicillins; in consequence the epidemiological advantage of reducing the likelihood of re-infection while the consort was being sought for treatment would be lost and the possibility of reducing the reservoir of syphilis would be lessened. The use of mixed "all-purpose" penicillins might provide the answer. Indeed in Dr. Willcox's hands there had been only 7·9 per cent. failures so far in 95 cases treated. On the other hand, the prolonged low-penicillin level produced by the benzathine penicillin component might itself encourage a lessened sensitivity. It was concluded at the Seminar that the present disturbing situation of increasing numbers of cases with an increasing proportion of failures to penicillin was likely to continue and that the dosage of penicillin (which was still regarded as a good drug in the treatment of gonorrhoea) to be recommended in gonorrhoea should be considered by the W.H.O. Expert Committee on Venereal Infections and Treponematoses at its next meeting. In the meantime, however, the dosage used, whatever the preparation, could with advantage be substantially increased.

DR. C. S. NICOL (*London*) said that he had been able to detect no difference, either clinically or with respect to the incidence of resistant gonococci, between whites and Negroes. The dosage of procaine penicillin which he used at present for the treatment of gonorrhoea was 600,000 units in one injection; an alternative was 1g. streptomycin in one injection with 5g. Sulphatriad daily for 5 days. He had been interested in Dr. Curtis's graph depicting the ideal blood levels of penicillin required for

the treatment of gonorrhoea; he thought that this pattern could be achieved only by means of multiple injections.

DR. A. GRIMBLE (*Guy's Hospital, London*) stated that his experience in London had been the same as that of previous speakers. In country clinics he had not seen one case of gonorrhoea that was resistant to 600,000 units penicillin.

DR. DAVID ERSKINE (*London*) said that he had found a large number of cases of penicillin-resistant gonorrhoea among merchant seamen in London. His laboratory reported cultures from these cases as penicillin sensitive: assay of the penicillin in use showed that it was up to potency and yet the cases did not respond. He had wondered if there was some other factor involved, but it now seemed that the technique in his laboratory might be at fault. Most cases which ultimately responded to treatment needed two injections of 300,000 units whereas one injection had been adequate until a few years ago. Larger and repeated doses would sometimes control refractory cases, but he often found it necessary to change over to streptomycin. Poor drainage from focal infection in the urethral follicles or prostate occasionally accounted for resistant cases.

DR. J. B. WOOLLEY (*Portsmouth*) stated that the few cases of gonorrhoea due to penicillin resistant organisms that he had seen in Portsmouth had been acquired in London.

MR. A. J. KING (*London*) noted that Dr. Curtis had described three categories of failures following the treatment of gonorrhoea; he could have described a fourth, that of sub-clinical failure. Was it not likely that this form had become more common. He and his colleagues had pointed out in 1950 (*Lancet*, 1950, **1**, 701) that some "cures" with penicillin were more apparent than real, but this evidence had been disregarded. It appeared late in the day to clutch at the straws of the pharmaceutical industry and the sulphonamides. Personally he was getting out his irrigation outfit and rescuing the fever cabinet from the lumber room.

DR. ERIC DUNLOP (*London*) said it gave him great pleasure to thank his colleagues for their important papers. The practice of giving "consolidation" treatment to patients suffering from syphilis might well have a bearing upon the emergence of resistant gonococci. It seemed an increasingly common practice to give such weekly injections of long-acting penicillin, including benzathine penicillin, after an initial course of anti-syphilitic treatment. Prolonged courses of this nature given to promiscuous persons might be an important factor in the emergence of strains of gonococci resistant to the action of penicillin.

DR. R. S. MORTON (*Stockport, Cheshire*) said that the outlook was indeed depressing, but that by looking in another direction, they might yet head-off the re-appearance of the douche can. For many years, many of them, while appreciating the usefulness of penicillin in the individual case, had recognized its limitations in the epidemiological control of gonorrhoea. What they had heard underlined that aspect dramatically.

Many infectious diseases had been controlled effectively by active immunization. It was 50 years since that aspect of gonorrhoea had been considered, and many advances had taken place in the field of immunology in the meantime. For example, fluorescent antibody techniques had been used in the localization of antigens. There had also been studies of the chemical composition of bacteria, with special reference to those components which might influence antibody production. So far as he knew the gonococcus had not been so studied.

It had generally been accepted that no animal except man was susceptible to the gonococcus. Why this should be so, would be worth learning, and indeed, herein might lie the secret. Stemming from the study of the difficulties of skin grafting, much had been learned about tissue immunity, and recent work gave some hints as to how such immunity might be overcome.

Furthermore, it had been noted that an animal that had been inoculated against one infection, might become more susceptible to another, and this might be used as a useful approach in attempting animal studies.

They were grateful for the prompt action that had set up a Medical Research Council Committee to look into the problem which they had been discussing. He would suggest that it would be reasonable to co-opt an immunologist to that Committee, so that the question of research into the possibility of active immunization against gonorrhoea might be discussed.

If any prophylactic vaccine were made available—and he felt that this would take some years—immunization should be made on a selective basis. Gonorrhoea was a disease of the big cities, and it would certainly be reasonable to inoculate prostitutes.

In the Manchester area, where some 20 per cent. of men with gonorrhea returned in the same year with at least one more infection, it would be reasonable to immunize all men attending with gonorrhoea. It might be possible to use the more promiscuous men as a measure of the usefulness of any prophylactic vaccine. As in other prophylactic campaigns, it should not be necessary to immunize 100 per cent. of the population to gain control.

DR. A. E. WILKINSON, in replying to the suggestions of previous speakers that the "tail" of relatively low penicillin concentrations produced by long-acting penicillin preparations might give conditions favourable to the emergence of resistant strains of gonococci, said that in the test tube it took some time to increase the resistance. He had grown a senstive strain of gonococcus in the presence of penicillin. At the beginning of the experiment it was sensitive to 0·008 units/ml.; after 3½ months its sensitivity was 0·125 units/ml., a sixteen-fold increase in resistance. He had not been able to detect a penicillinase in a small number of naturally-resistant strains. He felt that, if penicillin were to be used to treat patients infected with the more resistant strains of gonococci, some preparation such as Dr. Curtis had proposed was needed; it

must give a high blood level for about 30 to 48 hrs. and then be eliminated very rapidly to avoid a "tail" of sub-bacteriostatic concentrations.

In replying to Dr. R. S. Morton's suggestion that immunization might be a profitable line of investigation he said that, although a certain amount of work on the biochemical aspects of the gonococcus had been carried out, this had mainly been aimed at the development of serological tests. He felt that the gonococcus was a neglected organism and we still knew very little about it.

DR. F. R. CURTIS stated in reply that whenever a new drug was introduced careful research could always find some organisms with more than average resistance. An example was provided by Romansky, who found one strain of gonococci resistant to a concentration of 0·3 units penicillin. He was interested in Dr. Craddock-Watson's remarks about the sulphonamide sensitivity of gonococci, but he felt it would be a retrograde step to use these drugs again for gonorrhoea since the patients expected injections for the disease.

The incidence of gonorrhoea at the Whitechapel clinic had again increased in the first quarter of 1958 as compared with the same period in 1957. He suggested that the incidence of post-treatment gonorrhoea which occurred in the first week after therapy with penicillin should be reported in clinic returns. DR. Prebble had mentioned that he used streptomycin for almost all cases of gonorrhoea. In all probability he would be producing streptomycin-resistant organisms even faster than penicillin-resistant gonococci were being produced.

Finally, in reply to Mr. King, who had chided him for not including a subject dear to his heart—that of asymptomatic gonorrhoea—he said that he would deal with this point at length upon a later occasion; he would only say for the present that he had noted the phenomenon and felt that asymptomatic gonorrhoea could easily be produced.

REFERENCE

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